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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ESKETAMINE (SPRAVATO — JANSSEN INC.)
Indication: For the treatment of major depressive disorder in adults.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that esketamine not be reimbursed for the treatment of major depressive disorder in adults.

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ESKETAMINE (SPRAVATO — JANSSEN INC.)

Indication: For the treatment of major depressive disorder (MDD) in adults.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that esketamine not be reimbursed for the treatment of MDD in adults.

Reasons for the Recommendation

1. The results of two four-week randomized controlled trials (RCTs) (TRD3001 and TRD3002) and one randomized withdrawal study (TRD3003) did not demonstrate a consistent statistically significant benefit with esketamine in combination with a newly initiated oral antidepressant compared with placebo in combination with a newly initiated oral antidepressant, in the indicated population. There are several important limitations in the RCTs reviewed that cumulatively result in a high degree of uncertainty regarding the magnitude of the treatment effect of esketamine. Only one of the two four-week induction RCTs demonstrated a statistically significant difference between the esketamine and placebo groups for the primary outcome; there were no direct comparisons of esketamine with other known effective antidepressant therapies; patients in the trials initiated a new oral antidepressant simultaneously with esketamine; unresolved bias remained regarding the potential for unblinding in the trials; the RCTs were of a short duration relative to the duration of MDD; and an enriched population was enrolled across the studies. Due to these limitations, CDEC considered the magnitude of benefit of esketamine in clinical practice to be uncertain and potentially lower than the treatment effects estimated in the three RCTs.
2. The available RCTs were not designed and statistically powered to evaluate several important patient-valued outcomes such as improvements in patients' health-related quality of life, improvements in daily activities or functioning, reduced suicidality, and hospitalizations or emergency department visits.
3. It is unclear if the results of these trials are generalizable to a Canadian population because the patient population enrolled in the trials did not reflect those in whom esketamine would most likely be used in Canadian clinical practice. Esketamine would typically be used in clinical practice later in the treatment pathway than after non-response to only two oral antidepressants, though most participants in the included trials had an inadequate treatment response to two prior oral antidepressants.
4. The overall and long-term balance between the potential benefits and harms of treatment with esketamine are highly uncertain because of limitations with the clinical evidence. A greater proportion of patients who received esketamine in the RCTs experienced treatment emergent adverse events compared to the placebo group.

Discussion Points

- There is a clear unmet need for effective and safe treatments for patients who have not responded adequately to sequential optimized antidepressant trials. CDEC could not confirm that esketamine meets the unmet need of patients with an inadequate response to at least two separate courses of antidepressants. This is in part due to the uncertain meaningful benefit of esketamine in the studied populations overall, as well as the lack of data to identify people in whom esketamine is most likely to provide benefit.
- The CADTH systematic review included a third four-week induction placebo-controlled RCT, Study TRD3005, in patients aged 65 or older. Health Canada concluded that evidence of efficacy was not established in this study as the primary outcome did not demonstrate superiority of esketamine over placebo. As a result, esketamine is not recommended for use in patients aged 65 years or older.
- CDEC expressed concern regarding the potential risk of patients inappropriately receiving esketamine before other more suitable treatments, such as augmentation of oral therapies and non-pharmacological interventions. Drug plans are likely to have challenges in determining whether an individual received an adequate treatment with different antidepressants or other therapies before initiating esketamine. Data from the reviewed RCTs did not allow determination as to whether the doses of prior or concomitant oral antidepressant therapy were optimized or whether sufficient time was given for patients to experience a symptomatic improvement in their depressive symptoms.
- CDEC considered the patients enrolled in the reviewed RCTs to be a highly selective population. It was noted that patients with comorbid psychiatric disorders, recent suicidality, or substance use disorder may not be suitable for esketamine because such

individuals were excluded from the trials. However, in clinical practice those who are refractory to several antidepressants may also have comorbid psychiatric diagnoses, substance use disorder, or recent suicidal ideation or behaviours.

- Patients were randomized to receive esketamine or placebo four weeks after initiating a new oral antidepressant in Studies TRD3001 and TRD3002. CDEC noted that the requirement for patients to initiate two new treatments at nearly the same time — treatment with esketamine and a new oral antidepressant — after treatment non-response with a previous antidepressant was inconsistent with generally accepted clinical practice, where two medications are not typically started simultaneously. As well, four weeks of treatment with an oral antidepressant is likely an insufficient duration to achieve beneficial antidepressant effects. This design feature made it difficult to determine the magnitude of the benefit from either of the newly initiated treatments, and whether adverse events were due to either of the drugs or the combination.
- CDEC noted that the sponsor took certain steps to maintain double-blinding during the trials (e.g., bittering agent added to placebo, remote outcome assessors). However, potential impacts of unblinding related to other acute effects of esketamine, such as sedation, nausea, or cardiovascular changes, were not examined. Moreover, no evaluations regarding the extent of unblinding were conducted. CDEC agreed with the assessment from CADTH, other health technology assessment organizations (i.e., NICE, ICER), and regulators (i.e., Health Canada, EMA, FDA) that bias remained regarding the potential for unblinding in the trials for esketamine. Unblinding is of particular concern given the use of a subjective outcome measure (Montgomery-Åsberg Depression Rating Scale [MADRS] score).
- The optimal dosage and duration of therapy of esketamine could not be determined from the existing evidence. The limited longer-term data — primarily coming from two noncomparative, open-label extension studies — does not adequately address these questions. This lack of clarity has implications for the long-term balance of benefits and harms, as well as the costs of esketamine therapy.
- There are no data comparing esketamine with any relevant comparators; thus, CDEC could not determine whether esketamine provides superior, similar, or no clinical or economic benefit versus currently available therapies for MDD. Similarly, the trials were not designed to be able to determine whether esketamine should precede trials of combinations of antidepressants or augmentation of antidepressants with other medications (such as antipsychotic drugs, lithium, buspirone or stimulants), or nonpharmacologic therapies.
- CDEC considered the time commitment for patients to receive esketamine (e.g., remain under observation for two hours and refrain from driving for up to 24 hours) as a potential barrier for patients, particularly for those who must travel to the administration site to be under the supervision of a health care professional. The effects of treatment burden on outcomes and treatment adherence were not clearly identified in the reviewed studies.
- CDEC noted that misuse, abuse, or diversion of esketamine are potential concerns. The sponsor's controlled distribution program is intended to decrease the risk of adverse outcomes, including misuse or diversion of esketamine by patients. Details of the program are limited, and its potential effectiveness is uncertain.

Background

Esketamine has a Health Canada indication for use in combination with an SSRI or SNRI for the treatment of MDD in adults who have not responded adequately to at least two separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode. Esketamine is an antagonist of the N-methyl-D-aspartate receptor. It is available as a 28 mg nasal spray single use device. The Health Canada–approved initial dose is 56 mg for adults younger than 65 years of age. Recommended subsequent doses are 56 mg or 84 mg twice weekly for the first four weeks, then weekly for weeks five to eight. For weeks nine and onwards, the recommended dose is 56 mg or 84 mg weekly or every two weeks, based on the lowest frequency needed to maintain remission or response.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of RCTs of esketamine and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with MDD, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Four patient groups, the Mood Disorders Society of Canada (MDSC), the Canadian Mental Health Association (CMHA-National), the Alberta Division of CMHA (CMHA-AB), and the Mood Disorders Association of Ontario (MDAO) provided patient input, in two submissions, for this summary. The groups gathered information from patients with MDD and their caregivers through social media, online discussions, phone interviews, a focus group discussion, and online surveys. The following is a summary of key input from the perspective of the patient groups:

- Depression negatively impacts a patient's emotional, mental, and physical health; quality of life; and their ability to engage in day-to-day life. Some patients described experiencing stigma and social isolation as well as use of "negative coping" behaviours, including increased suicidal thoughts due to their depression. Relationships with family, friends, colleagues, and society were also reported to be negatively affected. The financial burden can be profound, as many patients are unable to work and must rely on disability payments or savings, may have limited access to government supports and resources, or have high out-of-pocket treatment costs.
- Although many treatments are available for depression, a substantial proportion of patients will not respond to multiple antidepressants, and treatment options for these patients are limited. Adverse effects can affect a patient's overall quality of life and willingness and ability to seek new treatments.
- Patients with treatment-resistant depression are seeking new treatments that can quickly provide sustained control of their depression symptoms, leading to improvement in routine functioning and overall quality of life. Approval of esketamine in Canada will be welcomed by patients with treatment-resistant depression; however, it is recognized that challenges exist in the use of this drug due to the time required for the treatment (esketamine should be administered in a health care provider setting) and difficult access to the drug (limited availability of the drug as well as its high cost). Equitable and timely access to a full spectrum of psychological support is critical for individuals when medication alone does not resolve depression.

Clinical Trials

The systematic review included three four-week double-blind RCTs (TRD3001, TRD3002, and TRD3005) and one double-blind, randomized withdrawal study (TRD3003) in patients with moderate-to-severe MDD who had an inadequate response to at least two prior antidepressant therapies of adequate dose and duration for the current major depressive episode. The number of patients enrolled in the trials ranged from 138 patients in Study TRD3005 to 705 patients in TRD3003, with 59 to 115 patients per randomized treatment group.

In the four-week induction studies, patients received intranasal esketamine (28 mg to 84 mg, fixed or flexible dosing) or placebo twice weekly, plus a newly initiated oral selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant. Two trials enrolled adults 18 to 64 years old (TRD3001 and TRD3002) and one trial enrolled patients 65 years or older (TRD3005).

The longer-term relapse prevention study (TRD3003) included adults with moderate-to-severe treatment-resistant depression who underwent two treatment phases with intranasal esketamine plus a newly initiated SSRI or SNRI (four-week induction phase and 12-week optimization phase). Those who achieved stable remission with intranasal esketamine (56 mg or 84 mg weekly or every two weeks) were randomized to either continue esketamine plus antidepressant or switch to intranasal placebo plus antidepressant in the maintenance phase. Patients who achieved stable response underwent a separate randomization to esketamine or placebo.

Key limitations were the relatively short duration of the RCTs, differential losses to follow-up in the induction studies (which in some analyses may inflate the treatment effects of esketamine relative to placebo), and potential reporting bias related to unblinding due to the frequency of acute adverse effects (e.g., sedation, dissociation, nausea, and cardiovascular changes) that are known to be associated with esketamine. The patients enrolled reflect an enriched population; thus, the studies' findings may overestimate the true benefits of esketamine in the real world. There is no direct evidence available comparing esketamine to other therapeutic options for patients with MDD who have not responded adequately to prior therapies.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed depression symptom severity (based on the MADRS), disability (based on the Sheehan Disability Scale [SDS]), response, remission, and relapse. The primary outcome in three trials was the change from baseline in MADRS total score at four weeks. Time to relapse in the stable remission population was the primary outcome in Study TRD3003.

- The MADRS is a physician-rated measure of the severity of depression symptoms. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. It is scored from zero to 60, with higher scores indicating more severe symptoms. There is evidence to support the validity of the MADRS, with a minimum clinically important difference (MCID) of 2 in patients with MDD.
    - Response was defined as a 50% or greater decrease in MADRS total score and remission was defined as a MADRS total score 12 or lower.
    - Relapse was defined as a MADRS total score 22 points or more for two consecutive assessments; or hospitalization for worsening depression; or any other clinically relevant event that was suggestive of a relapse of depressive illness as per clinical judgment (for example, suicide attempt, completed suicide, or hospitalization for prevention of suicide).
- The SDS is a three-item scale on which patients rate the extent to which their work, social life or leisure activities, and home life or family responsibilities are impaired by their symptoms (zero indicates no disability; 10 indicates extreme disability). Total scores range from zero to 30, with higher scores indicating more severe disability. The MCID is not known.
- Although health-related quality of life and suicidality were identified as key efficacy outcomes of interest to patients, none of the included studies were designed or powered to evaluate these outcomes.

Efficacy

One of the three four-week induction studies (Study TRD3002) reported statistically significant differences favouring esketamine over placebo for the change from baseline in MADRS total scores, with a least squares mean difference (LSMD) of –4.0 points (95% confidence interval [CI], –7.3 to –0.6; one-sided P = 0.010). The mean difference exceeded the MCID for the MADRS and was interpreted as clinically relevant by the experts consulted for this review. The two other induction studies reported changes from baseline in MADRS total scores that were similar in magnitude and direction, but with a 95% CI that included the null. The LSMD in Study TRD3001 was –3.2 points (95% CI, –6.9 to 0.5; one-sided P = 0.044; not significant) between esketamine 84 mg and placebo, and 4.1 points (95% CI, –7.7 to –0.5; significance not tested) for esketamine 56 mg versus placebo. In Study TRD3005, which enrolled patients 65 years or older, the LSMD between esketamine and placebo for the change from baseline in MADRS score was –3.6 points (95% CI, –7.2 to 0.07), which was not statistically significant with the one-sided P value of 0.029.

The study results for measures of disability, based on the change from baseline in SDS, were limited by the extent of missing data (20% to 25%), and uncertainty in the validity of and MCID for the SDS. For Study TRD3001, no statistically significant differences were found between esketamine and placebo; for Study TRD3003, statistical significance was not tested for the change in SDS due to failure of a prior outcome in the statistical testing hierarchy.

In the induction studies, the proportion of patients in the esketamine groups who met the criteria for response or remission was nominally higher than in the placebo groups, but no between-group comparisons were conducted. To evaluate the potential for rapid treatment response, two induction trials reported on the onset of clinical response by day 2 that was maintained to day 28. For study TRD3002, 8% and 5% in the esketamine and placebo groups, respectively, had onset of response by day 2, with no statistically significant differences between groups. In Study TRD3001, 10% and 9% in the esketamine groups versus 2% in the placebo group met the criteria for onset of clinical response by day 2. The analysis of between-group differences showed wide 95% CIs, which were inconclusive due to failure of a prior outcome in the statistical hierarchy.

Among patients who achieved stable remission at the end of the optimization period of Study TRD3003, 39 patients (45%) relapsed after being switched to placebo compared with 24 patients (27%) who remained on esketamine. Relapse was delayed in the esketamine group relative to placebo with a hazard ratio of 0.49 (95% CI, 0.29 to 0.84; P = 0.003). Among patients in the stable responder population, relapse was delayed for those who remained on esketamine compared to those who switched to placebo, with a hazard ratio of 0.30 (95% CI, 0.16 to 0.55; P < 0.001).

Harms (Safety)

In all of the reviewed studies, the proportion of patients who reported adverse events was higher for those who received esketamine (71% to 89%) than for those who received placebo (46% to 68%). The most commonly reported adverse events in the esketamine groups were dissociation, dizziness, vertigo, nausea, dysgeusia, somnolence, and increased blood pressure.

The percentage of patients who stopped intranasal study drug treatment due to adverse events ranged from 1% to 7% of patients who received esketamine and 1% to 3% who received placebo. Serious adverse events were reported by 0% to 4% of patients in the esketamine groups, and 0% to 3% of patients in the placebo groups during the four trials. Worsening depression, anxiety, suicide ideation, increased blood pressure, hypertensive crisis, cerebral hemorrhage, dizziness, vertigo, and sedation were among the serious adverse events noted.

The sponsor reported three completed suicides among patients with treatment-resistant depression who were treated with esketamine during the phase II and phase III trials (2.9 events per 1,000 person-years). No suicides were reported among those who received placebo (100 person-years).

Longer-term comparative safety data for esketamine is limited.

Due to the hemodynamic and cognitive adverse effects, and the abuse potential of esketamine, the drug will be available through a controlled distribution program, and administration of the drug must be supervised by a health care provider who is experienced and equipped to manage adverse events such as respiratory depression or cardiovascular events.

Indirect Treatment Comparisons

No indirect treatment comparisons of adequate methodological quality were identified in the literature or were provided by the sponsor.

Cost and Cost-Effectiveness

Esketamine is available as a 28 mg intranasal solution at a submitted price of $273 per dose. The recommended initial dose of esketamine for adults in combination with oral antidepressants is 56 mg (two 28 mg devices) followed by subsequent doses of 56 mg or 84 mg twice weekly for the first four weeks, then weekly for weeks five to eight. From weeks nine onwards, the recommended dose is 56 mg or 84 mg weekly or every two weeks, based on the lowest frequency needed to maintain response or remission. At the recommended dose, the annual cost of esketamine is between $18,546 and $45,591 in year 1 and $14,196 and $42,588 in subsequent years.

The sponsor submitted a cost-utility analysis comparing esketamine plus oral antidepressant with oral antidepressant alone. The sponsor's base case was conducted from the perspective of a Canadian publicly funded health care payer over a five-year time horizon. Patients started in the model in the resistant depression stage, which consisted of the acute phase (weeks 1 to 4), early maintenance (weeks 5 to 8), late maintenance (weeks 9 to 40), and recovery (weeks 41 and onwards). After this, patients could transition to the following health states: fail treatment and remain in the current depressive episode but initiate subsequent treatment; achieve a response or enter remission based on MADRS score; discontinue treatment; or, death. Patients could further improve or regress in terms of their MADRS score and subsequently transition to improved health states (i.e., remission or recovery) or deteriorated health states (i.e., loss of response, relapse, or recurrence). Treatment effects were informed using the TRANSFORM-2 and SUSTAIN-1 clinical trials.

CADTH identified the following key limitations of the sponsor's submitted economic analyses:

- Response and remission rates for oral antidepressants alone were inappropriately adjusted based on the assumption that additional health care visits would result in an elevated placebo effect.
- The assumption that patients achieving and maintaining recovery would discontinue esketamine due to improved outcomes is currently uncertain in clinical practice.

- Inclusion of suicide-related mortality was associated with uncertainty based on the clinical findings, and inclusion of both suicide-related and all-cause population mortality potentially overestimate mortality in the model.
- Long-term maintenance of the treatment effect for esketamine plus oral antidepressant was uncertain as current clinical information is available up to a maximum of 91 weeks.

The CADTH base case reflected changes to the following parameters: applying unadjusted response and remission rates for the comparator (oral antidepressant); removing discontinuation rates for recovery for esketamine plus oral antidepressant treatment; and removing all-cause population mortality. Multiple structural limitations that were identified could not be addressed by CADTH (e.g., treatment effect waning and the impact of partial responders). Due to a lack of clinical information, CADTH was unable to include relevant comparators such as IV ketamine or adjunctive treatments.

In CADTH's base case, esketamine plus oral antidepressant was associated with an incremental cost-effectiveness ratio of $125,376 per quality-adjusted life-year compared with oral antidepressant alone. At a willingness-to-pay threshold of $50,000 per quality-adjusted life-year gained, a price reduction of approximately 60% is required for esketamine plus oral antidepressant to be considered cost-effective. None of the scenario analysis reflecting different discontinuation rates for recovery or remission resulted in an ICER below $50,000 per quality-adjusted life-year gained.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

June 17, 2020 Meeting (Initial)

Regrets

None

Conflicts of Interest

None

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 9, 2020 Meeting (Reconsideration)

Regrets

One CDEC member did not attend

Conflicts of Interest

None